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October 26, 1999

MERCK
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Docket No. 99D-2635
Draft Guidance for Industry on ANDA's:
Blend Uniformity Analysis

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

As an innovative research and development company, Merck constantly explores new opportunities to improve the transfer of technology from the research laboratories to our manufacturing facilities. With a vision that validation is a continuum, Merck establishes a system of in-process controls and testing procedures during product development to ensure the quality of our marketed products. Thus Merck is affected by regulations which impact the in-process and finished product testing requirements to ensure product quality. For these reasons, we are very interested in and well qualified to comment on this Draft FDA guidance on ANDA's: Blend Uniformity Analysis.

General Comments

The proposed guidance reflects an issue discussed by FDA personnel during public presentations over the past few years. FDA refers to section of 21 CFR 211.110(a)(3) as the regulatory driver requiring blend uniformity analysis (BUA) during the manufacture of drug products. In summary, this section of the CFR states that manufacturers shall establish appropriate controls to monitor process performance and demonstrate adequate mixing to assure batch uniformity and homogeneity. The guidance document describes BUA as a "useful" test regime for assuring adequate mixing and recommends BUA be included as an in-process cGMP test requirement.

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We agree that uniformity of blends should be demonstrated as required by 21 CFR 211.110(a)(3). However, this requirement can be accomplished during validation of the blending process. The requirement for BUA as a routine in-process test regime conflicts in principle with the concept of process and blend validation. Implementation of BUA for a validated blending process in effect provides validation-type information with each batch. While this additional information may provide additional "comfort" that a blend is homogeneous, validation of the process/blend mix parameters is intended to provide the assurance of blend uniformity and routine analysis of each batch is unnecessary.

Problems associated with obtaining a representative sample of bulk powders are well known. PDA Technical Report 25 explores the issues associated with BUA, both during validation and as an in-process control parameter. Much of the report is dedicated to the difficulties associated with current limitations in sampling technologies. The report states "numerous publications cite the existence of sampling error in sampling large powder beds with thieves and the non statistically based criteria imposed on such samples . . . blend sampling at micro levels using existing sampling technologies often yields samples that are not representative of the product." Although obtaining representative samples of a blend has been demonstrated to be problematic, it is nevertheless difficult to invalidate a test failure and conclude that a sampling error occurred. This would result in the rejection of material that would result in, if processed to drug product, material that fully meets its quality and purity acceptance criterion.

While the concept of BUA could result in improved knowledge and control of a process, it would seem that the same information, namely blend homogeneity, could be gathered based on extended testing of the drug product. Performing extensive testing (10 intervals) for Content Uniformity across a batch of final product may provide the assurance intended to be provided by BUA. While neither approach should be necessary for a well controlled and validated process and the concept seems duplicitous with the concept of process validation, extensive product sampling and testing could be accomplished without the inherent risks associated with blend sampling.

The guidance document states that FDA intends to seek the support of the Product Quality Research Institute (PQRI) on the issue of BUA. PQRI is a collaborative process involving FDA's Center for Drug Evaluation and Research (CDER), Industry and Academia. The stated mission of PQRI is to conduct research to generate scientific information to support regulatory policy. It seems premature to issue a draft guidance document on BUA, where technical merit and sampling error are in question, before obtaining supporting data through PQRI.

Specific Comments

Page 2 – the document states that BUA "is not usually necessary" for drug product where the active is $\geq$ 50% of the drug product or where the active composition is $\geq$ 50 mg. The statement "not usually necessary" is very nondescript and could likely lead to differences in interpretation between FDA investigators.

Page 4 – Acceptance criteria for BUA is stated as 90 to 110% of label claim. This is much tighter than then final dosage Content Uniformity requirements of 85 to 115% listed in the USP. There is no justification for setting BUA acceptance criteria at this level.

Page 7 – the document defines "In-process Controls" as "tests that can be performed during the manufacture" of a drug. This very narrowly defines the term "controls" in the regard of testing, in this specific case as blend uniformity testing. However, a broader perspective must be applied to the term "in-process controls" to include in-process control parameters. This broader perspective more directly supports the fundamentals of process validation where appropriate "in-process parameters" are used to assure process control and consistency. "Blend testing" would only provide confirmation that the critical process parameters (such as blend time, revolutions, *etc.*) provided the "validated" level of control.

In conclusion, without careful consideration to the processing implications, routine blend uniformity analysis should not be a required in-process test on validated and well-controlled processes. The technical issues concerning blend uniformity analysis should be addressed through PQRI before further refining this draft guidance.

We trust that these comments will be considered in further development of the draft guidance.

Sincerely,

Dennis M. Erb

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